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De Novo Trisomy 16p

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We report on a patient with psychomotor retardation and a pattern of malformations comprising single umbilical artery, craniofacial anomalies, severe truncal hypotonia, and lower-limb hyporreflexia. G-banding cytogenetics demonstrated a 16p+ chromosome. Parental chromosomes were normal. The use of fluorescent in situ hybridization (FISH) showed that this extra material derived from chromosome 16. High-resolution G-banding demonstrated a duplicated segment on the 16p arm, confirming our suspicion of a de novo tandem duplication; hence, the cytogenetic diagnosis was given as 46,XY,dir dup(16)(p11.2→p12). Am. J. Med. Genet. 68:219–221, 1997 © 1997 Wiley-Liss, Inc.

KEY WORDS: chromosome 16; partial trisomy (16p); de novo

INTRODUCTION

Chromosome anomalies arising de novo are usually difficult to define, based on conventional cytogenetic analysis. Fluorescent in situ hybridization (FISH) [Pinkel and Gay, 1986] techniques have greatly contributed to overcoming this limitation, and most of these chromosomal rearrangements can now be properly identified.

Trisomy 16p is a rare finding that is being characterized as a distinctive syndrome. In this report, we describe clinically and cytogenetically a new case of de novo trisomy 16p.

CLINICAL REPORT

The propositus was a 23-month-old male, third son of a young couple with no relevant family or personal medical history, except that the mother suffered chronic pyelonephritis and was prescribed Tarivid® (ofloxacin), prior to fertilization and up to the second month of pregnancy.

Delivery was at term with clear amniotic fluid. A vacuum extraction was required during delivery. The infant weighed 3,700 g, cried spontaneously, and had a single umbilical artery. The patient's early history was normal, except for recurrent episodes of bronchitis and feeding problems.

At age 16 months he was referred to the Child Neurology Outpatient Department for tremor-like movements and ocular revulsions lasting several seconds, without loss of consciousness. The latter were more frequent when the patient was agitated. Physical examination showed (Fig. 1) a well-nourished baby, with a head circumference of 47 cm, occipital flattening, round face, very sparse eyebrows and eyelids, microphthalmia, narrow palpebral fissures, bilateral alternating strabismus, hypertelorism, epicanthus, long philtrum, cleft palate, anteverted and low-positioned ears, short neck, atopic body eczema, truncal hypotonia (but with normal muscular tone in limbs), moderate motor retardation, and right patellar and achillear hyporreflexia.

Psychomotor evaluation indicated a 58% delay for his age. He held his head at 7 months. Sitting and spontaneous turning over started at 16 months, the child being able to grasp objects and switch them from one hand to the other. He does not speak yet, merely producing guttural sounds. Motor activity is greater on the right side. Electroencephalogram was hypoactive for the patient's age, but no paroxysmal activities or epileptic foci were noted.

At present, the patient shows some behavioral abnormalities, resembling an autistic disorder and epilepsy.

CYTOGENETIC STUDIES

The chromosome analysis (50 mitoses) showed a 46,XY,16p+ karyotype. Subsequent analysis of more than 100 metaphases of maternal and paternal lymphocytes gave normal results (46,XX and 46,XY, respectively). Fluorescent in situ hybridization (FISH) analysis was then performed, using a digoxigenin-labeled whole-chromosome painting DNA probe (Oncor, Gaithersburg, MD) to chromosome 16. Hybridization and detection were performed according to the manufacturer's recommendations. The marker chromosome hybridized with the painting probe in its full length (Fig. 2). High-resolution G-banding (550 bands) demonstrated the existence of a direct-tandem duplication of

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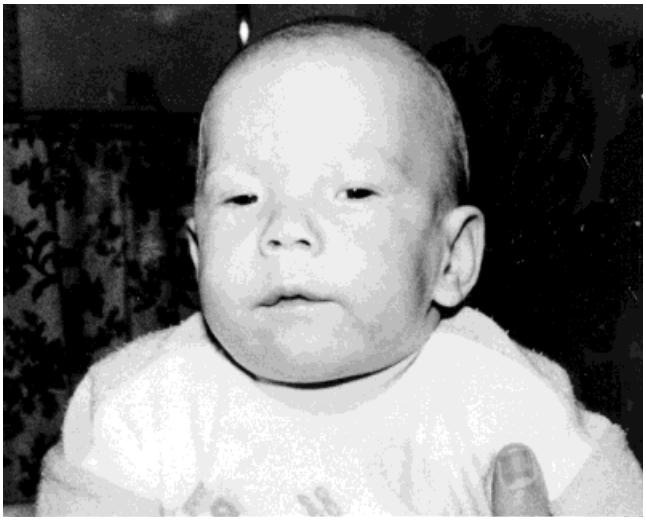

Fig. 1. Proband at age 6 months, showing typical facial appearance.

bands 16p11.2–16p12 (Fig. 3), and the karyotype could be described as 46,XY,dir dup(16)(p11.2→p12).

DISCUSSION

Trisomy 16p is a rare chromosomal anomaly, only 15 cases having been reported [Waterson, 1990]. As with almost all partial trisomies and monosomies, the alteration is usually secondary to a familial balanced translocation. However, 3 cases of de novo 16p duplication have also been described [Dallapiccola et al., 1979; Gabarrón-Llamas et al., 1981; Hebebrand et al., 1994]. Thus, the present case is the fourth such occurrence, since the chromosomes of both parents were normal.

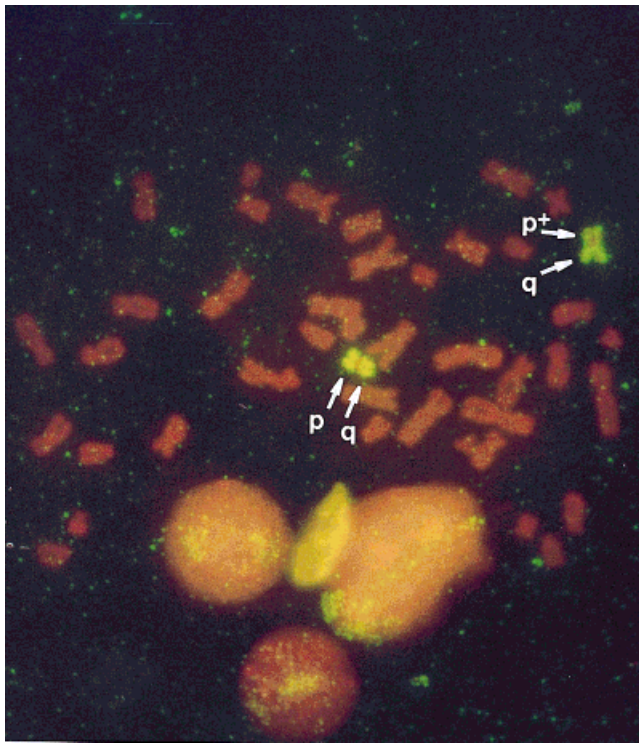

Fig. 2. Hybridization of digoxigenin-labeled whole-chromosome painting DNA probe (Oncor) to chromosome 16. Arrows indicate short (p) and long (q) arms of chromosomes of pair 16.

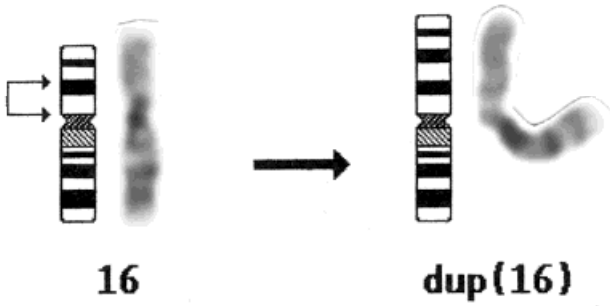

Fig. 3. Partial metaphase and idiogram showing dup(16)(p11.2 →p12).

An interesting point of the mother's history was the administration of Tarivid® (ofloxacin). The family inquired as to the possibility that the treatment had been the cause of the picture presented by the proband. Ofloxacin is a wide-spectrum fluorated quinolone which inhibits bacteria DNA gyrase, thus impeding DNA transcription to m-RNA. By analogy, it does not seem illogical to think that ofloxacin can exert a similar effect on the topoisomerase II of eukaryotic cells. However, studies both in vitro and in vivo show the absence of secondary effects of the product at cytogenetic level [Mitelman et al., 1988; Forsgren et al., 1989; Berkovitch et al., 1994]. Moreover, the drug may have also acted on the proband during the embryonic period leading to a chromosomic mosaicism, which was not our case.

As to the clinical picture, a consistent finding is a single umbilical artery, occurring in 3 of 6 cases, including the present one in which the umbilical cord has been described. However, this malformation is also a common finding in trisomies 13 and 18, as well as in nonchromosomal conditions [for review, see Jones, 1988]. Similarly, findings such as cleft or arched palate, inguinal hernia, severe neurologic disorder, cardiac anomalies, and respiratory complications are equally common in other trisomy 16p and other chromosome disorders. Perhaps the most significant and common aspect in trisomy 16p patients is their facial appearance, consisting of rounded face, sparse eyebrows and eyelashes, hypertelorism, epicanthus, very narrow palpebral fissures, a sleepy appearance, and anteverted low-set ears. This recurrence may constitute the more recognizable part of a putative 16p+ syndrome.

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